

LX. STUDIES ON KIDNEY FUNCTION.

I. THE RATE OF FILTRATION AND REABSORPTION IN THE HUMAN KIDNEY.

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Two rival theories of kidney function have for many years been under discussion: the secretion theory and the filtration-reabsorption theory.

The easiest standpoint to take is that the urine is secreted. If one supposes every single detail of the kidney function to be the result of vital activity governed by unknown laws, one may of course look upon any new fact brought to light with equanimity. It is, as Cushny says, an impregnable defensive position. The theory has varied somewhat but the variations do not in any essential differ from the original theory. In all its forms it is maintained that during moderate diuresis the water is secreted by the capsule of Bowman and that the more specific constituents of the urine are then added by secretion through the tubule cells. A serious objection against this theory and its modifications is that it is impossible to investigate them quantitatively. For this reason all quantitative work by their supporters has been done as critical attacks against the other theories with immediate retreat to the safe ground.

The other theory which has in later years been the basis of practically all experimental work on this question is the "modern theory" of Cushny [1917]. As it came out that Ludvig's view, that filtration in the capsules and mere diffusion processes in the tubules could explain the formation of urine, was untenable, the supporters of the theory had to admit that active vital work must be performed by the kidney cells. The work was supposed to be exerted by the tubules in reabsorption of water and that series of substances, the threshold substances, which are to a certain extent retained by the body because they are of some value for the organism. This theory was later simplified by Cushny's "modern theory," the main points of which are that fluid is filtered out in the glomeruli and that in the different cases different quantities of a fluid of a constant composition are reabsorbed by the tubules. The substances present in the reabsorbed fluid are the threshold substances and were supposed to be rather few in number, the rest being the no-threshold substances. This theory is excellently fitted for experimental study and has been used as basis for a number of experiments by the adherents of both

theories. The result has been a number of details explained differently according to the views held by the respective writers and the question as between the two theories is as undecided as ever.

In recent years one of the points in the "modern theory" which has been most discussed is the distribution of the different substances among the two groups: threshold substances and no-threshold substances.

According to the theory of Cushny all no-threshold substances must be concentrated to about the same extent during their passage through the tubules. If the concentration ratio for a substance falls less than for others, it means that this substance is a threshold body which is reabsorbed.

Mayrs [1922] studied in this way the concentration ratios of creatinine, sulphate, phosphate and urea in experiments on rabbits. Whilst the first three were concentrated to practically the same extent, urea was not concentrated to the same extent. From this Mayrs concluded that the first three are no-threshold bodies and that urea is a threshold body.

White [1923], from similar experiments on dogs, concluded that urea, sulphate and phosphate are eliminated mainly by secretion of the tubules.

Havard and Reay [1926] find that phosphates in man are not concentrated to the same extent as sulphates, and phosphates must therefore, according to Cushny, be regarded as threshold substances. But if the phosphates—as they and also Eichholz and Starling [1925] suppose—are present in the blood largely as a colloidal calcium compound it is evidently only the diffusible part of the substance which is involved in calculating the concentration ratio. As long as this question is undecided, and as long as it is not possible to determine the amount of free phosphate, results obtained on phosphates cannot be considered as conclusive.

In the experiments described in the present paper it is shown that ingested creatinine is concentrated by the human kidney to an extent not reached by any other substance. This would mean either that all other substances are threshold bodies or that creatinine, as held by Marshall and Crane [1924], is secreted by the tubule cells.

The present position of this part of the question is, then, that one has to admit either that many substances hitherto regarded as no-threshold substances, urea, creatinine, sulphates and possibly phosphates, are added to the filtrate from the glomeruli by secretion by the tubules, or that practically all substances are threshold substances which are partly reabsorbed by specific cells of the tubules.

The experiments show moreover, as those of Mayrs, that for the new "threshold substance" urea it is impossible to suppose reabsorption in constant concentration.

The result of these experiments thus completely robs the "modern theory" of its simplicity which was one of its main advantages. In reality the theory is now left in a state where one may turn against it the objection raised by Cushny against the secretion theory "that it endows the renal cells with powers of discrimination of a very high order."

The only difference in this aspect between the two theories is that whilst cells secreting have to choose between the substances present in the blood, reabsorbing cells must choose between substances present in the filtrate.

Need we then completely abandon the theory? I think it is too early. The formulation of the theory is, I think, seriously at fault in the way in which it distinguishes between threshold and no-threshold bodies. As I think that the correction of this error will perhaps make it possible to keep the main part of the theory, filtration-reabsorption, as the fundamental function of the kidney, I propose to publish in a series of papers the results of experiments performed in the hope of throwing new light on the way in which the reabsorption process in the tubules must work if reabsorption really occurs, and also of getting experimental facts which could be used to decide between the two theories.

The plan of the experiments was to study the amounts of different substances reabsorbed and the percentage in which they are reabsorbed. The first step in this direction is to calculate the amount of filtrate formed in the glomeruli and the amount of fluid reabsorbed, and the first part of the study deals only with this side of the problem.

As the aim of the experiments made it necessary to obtain repeated series of observations on a single subject it was almost impossible to use animals. For this reason all experiments reported here were made on myself.

The calculation of the amount of filtrate is possible if we have a substance filtered out through the glomeruli none of which is reabsorbed during passage through the tubules. Suppose A to be a substance of this kind and F to be the amount of filtrate formed in the capsules, U the amount of urine, A_P % the percentage of the substance A present in the plasma in a diffusible state, and A_U % the percentage in the urine; then

$$(1) \frac{F \times A_P \%}{100} = \frac{U \times A_U \%}{100}.$$

This gives

$$(2) F = \frac{A_U \%}{A_P \%} \times U = C \times U.$$

when $\frac{A_U \%}{A_P \%} = C$ (index of concentration).

If R is the amount of fluid reabsorbed, then

$$R = F - U = C \times U - U = (C - 1) U.$$

The most difficult problem in planning the experiments was to select the substance to be used as a basis for the calculations. For a single day it is possible with fair accuracy to estimate the concentration of the urine by means of the colour—but it is impossible to compare the results from different days, as nothing is known about the constancy of the excretion of the specific coloured substance; on the contrary, the excretion is known to vary with the ingestion of meat and green vegetables. Urea of course becomes concentrated

to a considerable extent so that it would be reasonable *a priori* to suppose it to be a no-threshold substance which is not reabsorbed. However, the experiments by Mayrs showed that it was reabsorbed in appreciable amounts. Sulphate would be very difficult to use because of the difficult technique of its estimation.

The substance with the highest concentration ratio according to the values usually given for blood and urine is creatinine. The amount of creatinine in blood is, however, so small that the estimation of it is very uncertain. Behre and Benedict [1922] have even doubted its existence in the blood, a view which would imply that the amount of creatinine normally excreted by the kidneys should be synthesised by the kidneys themselves from a precursor in the blood. For this reason it was not advisable to rely upon the normal "preformed creatinine" in blood as a basis for the calculations. It was, however, decided to try if it was possible to raise the creatinine content of the blood by ingestion of creatinine, in order to see if this ingested creatinine could be eliminated by the kidneys as readily as the quantity supposed to be naturally present in the circulating blood.

The creatinine of the blood rises after the ingestion of about 5 g. creatinine to values of about 8 mg. or more per 100 cc. of plasma so that it can be estimated with tolerable accuracy, and the amount excreted through the kidney is relatively as great as that excreted normally. The creatinine content of normal human blood is given as between 0.7–1.5 mg. per 100 cc. This corresponds to an excretion of creatinine of 20–30 mg. per day per kg. bodyweight or about 1 mg. per kg. per hour. This gives for my bodyweight an excretion of 80 mg. creatinine per hour which is equal to the content of 5,300–11,400 cc. of blood if we accept the values given above. In the experiments to be discussed later the excretion per hour has, after ingestion of creatinine, varied in amount between values equal to 5,000–12,000 cc. of plasma or about 6,000–14,000 cc. of blood as experiments showed that the creatinine content of the blood was 85–90 % of the percentage in the plasma. The fact that ingested creatinine is eliminated by the kidney with the same readiness as that usually termed "preformed creatinine" points, I think, to the conclusion that the main part of the colour-producing matter in blood is really creatinine. If this were not the case, the kidney should synthesise creatinine at such a rate that the same rate of elimination was simulated.

Since a preliminary experiment of this kind showed that ingested creatinine is concentrated by the kidney to a far greater extent than any other hitherto observed substance in the urine, it was decided to use creatinine as the basis for the calculations after increasing the amount in the blood by ingestion of the substance.

Plan and methods of experiments.

In the morning 5 g. creatinine dissolved in 200 cc. of tepid water were taken by mouth. During the next hour other substances (urea, sodium

chloride, etc.) could be taken if it was wished to study the effect of a high blood content on the excretion of such a substance. No blood samples were taken until about an hour after the ingestion, as this early period cannot be used for the calculations aimed at in these experiments because of the great change in the creatinine content of the blood.

The samples of blood were drawn from the pulp of a finger by means of a spring blood lancet after scrubbing the hand with hot water. Enough blood is easily obtained in this way and it is mainly arterial. As only that part of a substance which is present in a free, diffusible state in the plasma can filter out through the glomerular membrane, it was necessary to use plasma for the determinations. The blood—about 3 cc.—was centrifuged very rapidly. In about 10 minutes enough plasma was obtained for the estimation of the different substances. The methods used in the estimations are described below. Immediately after taking the first blood sample the bladder was emptied and then samples of blood and urine were taken throughout the day. Samples which could not be analysed immediately were placed as soon as possible in the ice-chest.

Blood samples were drawn at intervals of about $\frac{3}{4}$ –1 hour, whilst urine samples were taken at varying intervals according to the diuresis.

The determination of creatinine in the plasma samples was carried out practically as in the original Folin method for whole blood [Folin, 1914]. To 1 cc. of plasma are added 5 cc. of a saturated solution of picric acid and a small amount of dry picric acid. The whole is vigorously shaken and left for at least half an hour with occasional shaking. At the same time 1 cc. of a standard solution of creatinine containing either 0.05 mg. or 0.1 mg. in 1 cc. is treated in the same way. Both solutions are then filtered and 2 cc. of each are measured into test tubes. To each tube and to 2 cc. of the saturated solution of picric acid is next added 0.1 cc. of a 10 % solution of NaOH. After the lapse of 5 minutes 2 cc. of water are added to each tube in order to get enough fluid for comparison and the solutions are then compared in the colorimeter. The colorimeter used was the new Leitz colorimeter (system Bürker). This system is especially suited to creatinine determinations as it allows the complete compensation of the colour produced in the picric acid itself by the addition of the alkali. The main principle in the colorimeter is that the light rays are sent through exactly the same layers of fluid on both sides. When, for example, the left-hand ray passes through a certain thickness of the unknown creatinine solution, the right-hand ray passes at the same time through a layer of the alkaline picric acid of the same thickness. The right-hand ray then passes through a layer of 1 cm. of the standard solution and the left-hand ray at the same time through 1 cm. of the alkaline picric acid. In this way the only colour difference is due to the creatinine content in the two solutions compared. For this reason the picric acid used has been recrystallised only once from hot water.

The creatinine in the urine was determined in much the same way. The

sample of urine to be estimated was diluted according to the expected concentration of creatinine (which was judged by means of the time interval since the ingestion of the creatinine and the urine volume) so that the content was approximately 0.5–1 mg. in 1 cc. To 1 cc. of the urine so diluted, to 1 cc. of water and to 1 cc. of standard creatinine solution containing 1 mg. in each cc. were added 5 cc. of the saturated picric acid solution and 1 cc. of a 10 % NaOH solution. After the lapse of 5 minutes, 5 cc. of water were added and the solutions compared in the same way as in the blood analyses.

The ingestion of 5 g. creatinine leads to an abrupt rise in the creatinine content of the blood. The rise itself has not been studied, as blood samples have seldom been taken during the first hour; but after the lapse of an hour or so the content of the plasma is usually about 8 mg. in 100 cc. The percentage now falls during the following hours and is usually 3–4 mg. per 100 cc. of plasma 6–7 hours later. (Compare curves for plasma creatinine, Fig. 1.)

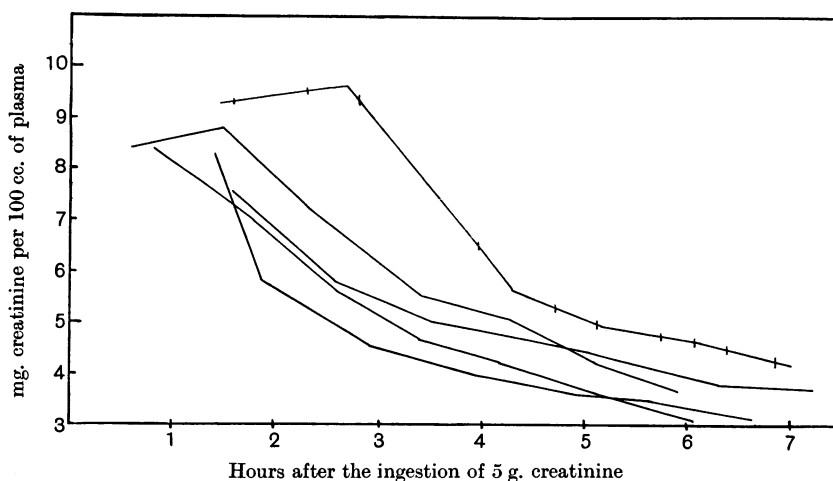


Fig. 1. Curves of plasma creatinine after ingestion of 5 g. creatinine.

The calculations are made in the following way. On the curve for plasma creatinine the times for the taking of the different urine samples are marked (as in the upper curve of Fig. 1) and the values for plasma creatinine corresponding to the different intervals are read off from the curve. No regard has been paid to a possible displacement between the intervals to be compared owing to the quantity of urine to be expelled from the "dead space" of the uriniferous system.

The influence of this displacement will be that the urine collected during a certain interval has its origin from a glomerular filtrate derived from a blood with a different composition from that existing when the urine reaches the bladder. The magnitude of this delay depends evidently on the volume of the "dead space" and the diuresis in each single case. The volume of the "dead space" consists of the capsules, tubules, collecting tubes, renal cavities

and ureters. The volume of these certainly varies according to the diuresis in each case, the number of glomeruli functioning, the filling of the renal cavity, etc. The main error is probably due to the amount of urine stagnant in the renal cavity, but this error, as well as that due to the volume to be expelled from the tubules, it is impossible to calculate with any accuracy. The error will, however, in all cases be that the urine is compared with blood with a creatinine content which is lower than that of the blood from which the urine is really derived. A displacement of 10 minutes will, however, scarcely be perceptible and a delay of this length of time is not likely to occur except during very slow diuresis. During slow diuresis the error may, of course, be quite definite but as it is impossible to estimate its magnitude the possible displacement has been disregarded even in these circumstances.

The concentration index is now calculated from $\frac{Cr_U \%}{Cr_P \%}$ and the amount of filtrate from $C \times U$.

The rate of the filtration.

The extent to which the creatinine has been concentrated by the kidneys has of course varied very much in the different experiments. The lowest concentration index ($C = \frac{Cr_U \%}{Cr_P \%}$) met with has been 7.7, a result obtained with a diuresis of 19.25 cc. per min. Although no attempt has been made to raise the concentration index by reducing the fluid intake, it has reached the high value of 293 with a urine production of 0.44 cc. per min. No doubt it would be possible to drive the concentration index even higher.

The excretion of creatinine varies roughly with the creatinine content of the plasma (compare Fig. 2). In the majority of experiments the excretion per minute has been equal to the amount of creatinine in 110–150 cc. of plasma. The amount of filtrate formed seems, therefore, to be rather constant during a moderate diuresis and should for my kidneys vary between these two values. In a number of experiments with big diuresis the amount of creatinine excreted has, however, been equal to a plasma volume of nearly 200 cc., whilst on the other hand the excretion sometimes falls to an amount equal to only 80 cc. of plasma, and in one case, as a sequence to a violent diuresis produced by urea ingestion, the calculated filtration went down to 57 cc. per min.

To understand these values it must be added that the creatinine was taken in 200 cc. of water and that lunch, including a fluid intake of 300 cc., was taken as usual during the experiments, so that none of the observed values can be regarded as corresponding to a resting kidney. The calculated filtration may probably fall far below any of the values here observed.

How do these creatinine excretions fit with the two theories? According to the filtration-reabsorption theory the values obtained depend upon the amount of filtrate formed in the glomeruli. According to the secretion theory they only indicate the power of the kidney to secrete creatinine. Both theories

have a limit for what they can explain in the rate of the necessary flow of blood. The filtration-reabsorption theory requires that the calculated amount of filtrate should not be higher than the amount which can possibly be formed from the flow of blood through the glomeruli. The secretion theory cannot explain the excretion of more creatinine than the amount obtainable from the flow of blood which we can assume to have taken place through that part of the tubules responsible for the excretion of creatinine.

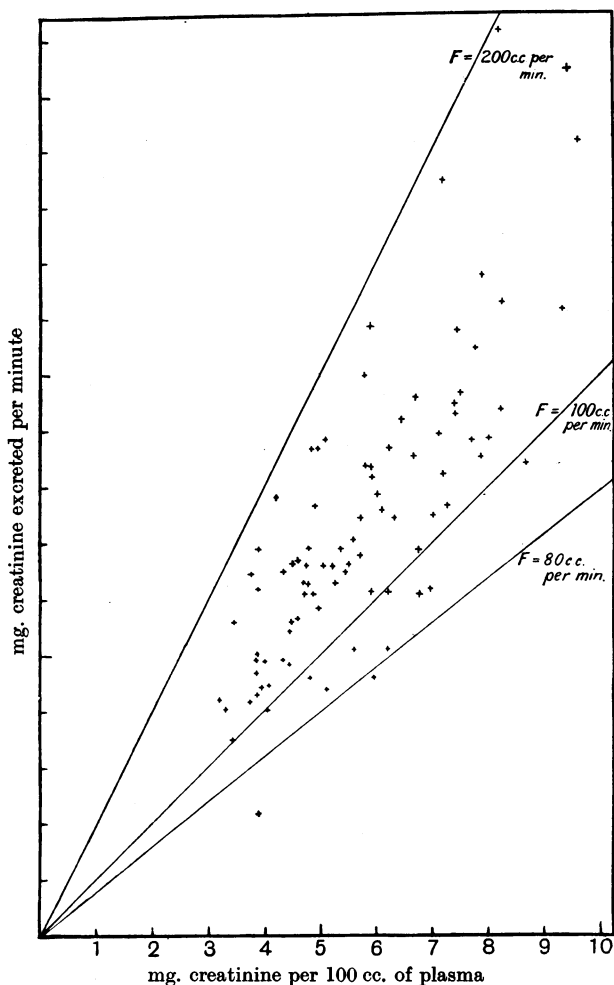


Fig. 2. The excretion of creatinine compared with the plasma creatinine.

Is it possible to filter out from the blood passing through the glomeruli quantities of fluid as large as 200 cc. per min.? A filtration of this magnitude has only occurred when the blood was diluted through excessive water drinking and in such circumstances I think it quite possible to filter out about one-third of the water from the plasma which will require a blood flow of about 1 l. per min.

This is a blood flow of the magnitude to be expected during a violent diuresis. In experiments on rabbits by Hayman and Starr [1925] the maximum blood flow per minute was 3.7 cc. per g. kidney, corresponding to a current of more than 1 l. per min. through the two human kidneys assumed to weigh 150 g. each. There is therefore no doubt blood enough available for filtration of this amount of fluid. Another problem is whether it will be possible to drive such an amount of fluid through the tubules.

If we do not take into account the possibility that the striated border in the proximal convoluted tubules can help to drive the fluid along, a possibility which cannot be absolutely rejected even in the case of the mammalian kidney, we have only the pressure existing in the cavity of the capsule as motive force. Is this pressure high enough to drive the fluid through the tubules? To answer this question is very difficult. Brodie [1914], who studied it, came to the conclusion that the pressure needed to drive out the urine alone was so high that it should not be possible to obtain it in the capsule as the result of filtration, and for this reason he put forth a theory of the glomerulus as a propulsive motor. The estimation of the necessary pressure is very problematic since according to Poiseuille's law the pressure needed to drive a certain amount of fluid through a capillary tube is proportional to the fourth power of the diameter, so that small errors in the diameters assumed have a very large influence on the result.

If we estimate the number of glomeruli in both kidneys at 2,000,000¹, the observed maximum filtration is $200 \times \frac{1}{2} \times 10^{-6}$ or 10^{-4} cc. = 0.1 mm.³ per min. per glomerulus, whereas the observed maximum diuresis is about 20 cc. or 0.01 mm.³ per glomerulus per min., so that only one-tenth of the filtrate reaches the collecting tubes.

Now we know next to nothing about the lumen in the tubules of the human kidneys during diuresis, but in rabbits the lumen of the proximal convoluted tube is, during diuresis, about one-third of the outer diameter (measured on fixed material [Jessen, 1923]). The outer diameter of the proximal convoluted tube of the unfixed human kidney is according to Peter [1909] about 65 μ , so that the lumen should, during diuresis, be about 20 μ . The length is, according to the same author, about 14 mm. To drive the total amount of fluid (200 cc.) through the whole length would, according to Poiseuille's law, require a pressure of about 32 mm. Hg. To calculate how much pressure is needed to drive the fluid through the rest of the tubules is practically impossible as we do not know where the main reduction in volume occurs—possibly it takes place to a large extent already in the proximal convoluted tubules.

To drive the whole amount of fluid through the tubules, however, would be impossible as this would require a pressure of about 100 mm. Hg even if the tubules had a diameter of 20 μ , which is not likely to be true for the whole

¹ A study of the number of glomeruli in the human kidney by Dr Vimtrup is in progress. The above number is a preliminary minimum estimation by him.

length. To drive the resulting 0.01 mm.³ urine through tubules of 15 μ diameter will, however, require only an additional pressure of 32 mm. Hg: so that if the main reduction in volume occurs in the proximal convoluted tubes and the first part of Henle's loop, we should in all require a pressure of about 65 mm. Hg. If we assume an average blood pressure of 120 mm. Hg, this leaves 55 mm. From this we have to subtract 25–35 mm. for the osmotic pressure of the colloids of the plasma so that we have a pressure of 20–30 mm. Hg for driving the blood from the aorta to the glomeruli and for the filtration. The calculation is not worth much inasmuch as Poiseuille's law does not hold for elastic tubes but will give too high values for the calculated pressure; but what one can say is: (1) that there is not pressure enough to drive the whole amount of filtrate out; (2) there is enough, however, to drive it part of the way and the resulting urine the rest of the way. During the usual moderate diuresis the pressure needed is of course much lower and easily available.

The conclusion arrived at is that the calculated amount of filtrate, though it turns out to be even larger than formerly supposed, is not of a magnitude which makes the conception of a filtration impossible. There is a sufficient blood-flow to account for the filtration and a sufficient pressure to account for the flow of urine. On the other hand, it will be very difficult to explain by secretion the excretion of the large quantities of creatinine observed. It is generally accepted that the total volume of blood flowing through the kidneys is available for the excretion of any substance according to the secretion theory; but this view is certainly not tenable. The secretion theory must explain—and does so—the differentiation of the tubules in different parts by assuming that the different parts are provided with the capacity to secrete specific substances. When creatinine is excreted in quantities corresponding to the content of 200 cc. of plasma per min. the cells responsible for the secretion of this substance must evidently have had a blood supply of 300 cc., even if we assume—what is very unlikely—that the cells are perfectly efficient in taking up from the blood and secreting creatinine. At the same time, however, urea is excreted corresponding to 200 cc. of blood, sulphate in about the same amount, uric acid and phosphates corresponding to about 100 cc. of blood, not to speak of the many other constituents of the urine; so that even if we admit perfect efficiency in secreting these substances, the cells responsible for their excretion will need all the blood which we can expect to flow through the kidney; and of this flow one-quarter to one-third must flow through the part responsible for the secretion of creatinine. Is this possible?

After the results of Traut [1923] and Langley [1925] it is evident that practically the total amount of blood flowing through the kidneys passes through the glomeruli. Arteriae rectae feeding the tubules directly are only present in quite insignificant numbers. This blood flow, after leaving the glomeruli through the efferent vessels, breaks up into a number of capillary channels forming a network round the tubules; but with this distribution of the blood flow it is hardly possible that any single part of the tubules will

receive more than a fraction of the blood flowing through the glomeruli. If this be so, then either the different parts of the tubules are not specific as regards secretion of the different substances but must function as a whole—a view which is not likely when the highly specialised epithelium is considered—or the only place where these substances can be excreted is the glomeruli. For other substances which are not excreted in such large quantities, the blood flow through the tubules may of course be sufficient to allow of their excretion there; but if the creatinine is excreted through the glomeruli by filtration—and I see scarcely any other possibility—then the amount of filtrate necessary to excrete the creatinine will contain all other diffusible substances to be excreted in greater quantities than the resulting urine, so that no secretion in the tubules is required. I think that the result of these experiments as regards creatinine excretion is a very strong argument in favour of the theory that the function of the glomeruli is the formation of a large amount of filtrate. This view is still more emphasised by the structure of the glomeruli. The general conception of the capsule of Bowman, given by Cushny, is “a hollow sphere of very delicate epithelium, one side of which is invaginated by a closely twining nodule of capillaries and arterioles, until the cavity is almost entirely obliterated.” If filtration should occur in such a structure, the fluid would have to filter out first through the capillary endothelium into the cavity between capillaries and the inner epithelium of the capsule and from there through the inner epithelium into the cavity.

In reality it is not so. In a recent paper Vimtrup [1926] demonstrates that the inner epithelium follows each single capillary as the finger of a glove follows the finger of the hand. This gives conditions much more favourable for filtration than those generally assumed: there is no space between the capillaries and the inner epithelium, the fluid must filter only through the single very delicate membrane consisting of capillary endothelium and capsule epithelium. Vimtrup¹ estimates the surface of a glomerulus at $442,000\mu^2$ (minimum). For the 2,000,000 glomeruli in both kidneys this gives a surface of at least 8800 cm.^2 . If we filter out 200 cc. per min. through this surface it gives a filtration rate of 4μ per sec.

This is a very rapid filtration, but that a filtration of this magnitude is possible is shown by the results of Wearn and Richards [1924] who obtained in the frog, where the surface of the glomeruli is not nearly so large as in the mammalian kidney, as much as 1.5 mg. filtrate from one single glomerulus in an hour. The maximum filtration rate in these experiments is about 200 cc. in a minute or about 6 mm.³ in an hour for one single glomerulus.

The result of these considerations is therefore that a filtration of 200 cc. per min. is possible; the blood flow is sufficient and it is in reality easier to understand the excretion of so many substances in amounts corresponding to large volumes of blood by supposing them all to be excreted along with the same quantity of water through the glomeruli.

¹ Private communication.

The quantity of fluid reabsorbed.

If we now study the amounts of fluid which according to the theory must have been reabsorbed in the different experiments, the result is that the amounts have varied, within practically the same limits as the filtration, between 50 to 200 cc. per min.

One of the main objections raised by the adherents of the secretion theory against the filtration-reabsorption theory is that such large quantities of fluid have to be reabsorbed. This is considered to be impossible or at least thought to be so unpractical that this consequence is by many deemed sufficient to condemn the whole theory; and the quantities which are usually assumed are not nearly so large as those reported in the present paper (about 40 cc. against a maximum here of 200 cc. per min.). Is such reabsorption really possible or is it so large that it is necessary for this reason to reject the theory? It is a fortunate fact that though it may be deemed unpractical it has been demonstrated clearly that it is by no means impossible first to have quantities of fluid of the order here considered excreted and then to have nearly all the water reabsorbed.

The urine of the bird is ejected from the cloaca together with the faeces as a paste. The experiments of Sharpe [1913] and Loye [1914] show, however, that the urine enters the cloaca from the ureter as a thin fluid the water of which is mainly reabsorbed from the rectum and the cloaca. In this way large quantities of water circulate—they are excreted through the kidneys and volumes comparable to the filtrate from the mammalian glomeruli are, as a matter of fact, reabsorbed by the wall of the cloaca. Loye states that a goose of 3 kg. bodyweight produced 2 l. urine from the ureter in 24 hours. Here we have an absorption from the cloaca alone which is equal to two-thirds of the bodyweight in 24 hours. Sharpe states that he has obtained from 10 cm. of the rectum and cloaca of the hen a reabsorption of $\frac{1}{3}$ cc. per min. The surface is not given, but I have measured the total surface of the cloaca of a hen with the bodyweight 2.3 kg. It amounted to 62 cm.² and must be able to reabsorb the total amount of ureter urine, which according to Sharpe may amount to as much as 1000 cc. in 24 hours or more than 11 mm.³ per cm.² surface per min.¹.

From the calculations of the pressure we should expect the main reabsorption to occur in the proximal convoluted tubules. If we assume 2,000,000 of them, a length of 1.4 cm. each and a diameter of 20μ we get a surface of

$$2\pi \times 10 \times 1.4 \times 10^4 \times 2 \times 10^6 = 17.6 \times 10^{11} \mu^2 = 17600 \text{ cm.}^2.$$

With the same power of reabsorption as the cloaca of the bird this surface should be able to reabsorb more than 190 cc. per min. or about the same quantity as observed in these experiments.

¹ This mechanism with the main reabsorption in the cloaca instead of in the kidney may perhaps be explained, as also suggested by Mayrs [1924], by the circumstance that it would be impossible for a bird to concentrate the urine to any greater extent in the kidney without stopping the flow in the tubules by sedimented uric acid. The large volume of water is needed to wash the uric acid out of the kidney and in order not to lose the large amount of water a secondary reabsorption in the cloaca has been developed.

The different forms of diuresis.

If we compare the amount of urine with the amount of filtrate from which it originates and with the extent to which it has been concentrated, we find that a diuresis may be produced in different ways.

Theoretically we may expect the following.

(1) The number of kidney units (glomeruli-tubules) working may be increased by opening of the blood flow through glomeruli hitherto closed as in the observations of Richards and Schmidt [1924]. That the number of open glomeruli varies also in the mammalian kidney is shown by Hayman and Starr [1925]. They find that in the normal kidney of the rabbit 60-90 % are open. If the work of each unit continues unaltered, the amount of urine will be increased but the composition will remain the same if the composition of the blood is not altered.

(2) The filtration through the glomeruli already open may increase. If the reabsorption is not increased to the same extent, the result will be a larger amount of urine less concentrated than before.

(3) The filtration may be the same, but the reabsorption less.

(4) The diuresis may result from a combination of these mechanisms.

If it is true that the amount of creatinine excreted may be taken as an index of the amount of filtrate formed and the concentration ratio of the creatinine as an index of the concentration ratio of the urine, we are now able to distinguish between these different forms of diuresis.

As examples I shall give the following abridged part of the calculations of an experiment.

Time	Cr_p %	Cr_u %	$C = \frac{Cr_u \%}{Cr_p \%}$	U	$F = C \times U$	$R = F - U$
10.50-11.37	7.45	636	85	1.69	145	143.3
11.37-12.11	6.50	801	123	1.15	142	140.9
12.11- 1.12	5.88	855	145	0.98	142	141.0
1.12- 2.30	5.30	972	183	0.80	146	145.2
2.30- 3.16	4.88	729	150	0.80	120	119.2
3.16- 4.15	4.42	725	164	0.67	110	109.3
4.15- 5.13	4.02	723	180	0.56	101	100.4

Cr_p % = mg. creatinine in 100 cc. plasma

Cr_u % = mg. creatinine in 100 cc. urine

C = concentration index

U = amount of urine in cc. per min.

F = amount of filtrate in cc. per min.

R = amount of reabsorbed fluid in cc. per min.

In this example we see that though the amount of filtrate from 10.50 to 2.30 is constant the amount of urine decreases. The conclusion is that the number of kidney units functioning is practically the same, but the tubules concentrate the filtrate more and more. From 2.30 the amount of filtrate begins to decrease so that the amount of urine falls still more. If we compare the fourth sample of urine with the last, we find that in the first case we have a production of urine of 0.80 cc. per min. from an amount of filtrate of 146 cc., in the last case we have from 101 cc. of filtrate an amount of urine of 0.56 cc. per min.

In these two cases we may imagine that a certain number of glomeruli have been closed, thereby reducing the amount of filtrate, but the remaining units have concentrated the filtrate to the same extent (180 times against 183).

A curve illustrating the influence of water drinking on the reabsorption and filtration is shown in Fig. 3.

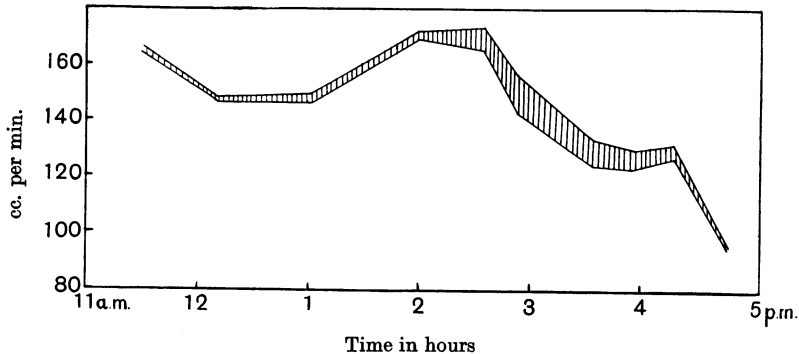


Fig. 3. The influence of drinking 1500 cc. of water on the rate of filtration (upper curve) and reabsorption (lower curve). The area between the two curves represents the diuresis. The water was taken at 1 o'clock.

In other examples we may find for instance a diuresis of 1.70 cc. per min. with a filtration in one period of 111 cc. per min. and in another of 143 cc. Though the diuresis is the same in the two cases, the extent to which the urine has been concentrated is quite different.

To understand the way in which the reabsorption works it is necessary to take into consideration these different ways of obtaining a diuresis. The plan for a study of kidney function outlined in this paper offers a method by which the changes may be followed.

SUMMARY.

(1) The filtration-reabsorption theory is discussed. Its present state calls for a thorough modification, or for the complete abandonment of filtration as the main factor in excretion by the kidney.

(2) The amount of creatinine present in the urine of man after ingestion of this substance is so large that it requires a filtration of up to 200 cc. per min. to explain it.

(3) The possibility of this is discussed and the result is taken to be in favour of the filtration theory.

(4) The surface available for reabsorption in the proximal convoluted tubes alone is so large that, provided it shows only the same power of reabsorption as the cloaca of the bird, it may reabsorb the whole quantity of fluid required in the concentration process in the tubules.

(5) The different ways in which a diuresis may be obtained according to the filtration-reabsorption theory are enumerated and discussed with examples.

(For references see the following paper.)